EASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'LIFESCI' ENTERED AT 15:11:03 ON 06 FEB 2006

FILE 'BIOTECHNO' ENTERED AT 15:11:03 ON 06 FEB 2006

FILE 'EMBASE' ENTERED AT 15:11:03 ON 06 FEB 2006


```
=> s D-serine (w) dehydratase
L1          251 D-SERINE (W) DEHYDRATASE

=> s hydantoinase
L2         1118 HYDANTOINASE

=> s l1 and l2
L3            0 L1 AND L2

=> s l1 and l2
L4            5 L1 AND L2

=> d ibib abs l4
```

L4 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:100428 BIOSIS
DOCUMENT NUMBER: PREV200500098289
TITLE: D-amino acid tolerant hosts for D-**hydantoinase** whole cell biocatalysts.
AUTHOR(S): Turner, Robert J.; Aikens, John; Royer, Sylvain; DeFilippi, Louis; Yap, Abigail; Holzle, Denise; Somers, Neil; Fotheringham, Ian G. [Reprint Author]
CORPORATE SOURCE: DeCODE Genet, 2501 Davey Rd, Woodridge, IL, 60517, USA embral@mac.com
SOURCE: Engineering in Life Sciences, (October 2004) Vol. 4, No. 6, pp. 517-520. print.
ISSN: 1618-0240 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2005
Last Updated on STN: 9 Mar 2005

AB Whole cell biocatalysts which enable the concerted use of D-**hydantoinase**, D-carbamoylase, and racemase enzymes are valuable for the production of D-amino acids. However, Escherichia coli host strains used for this purpose efficiently degrade D-amino acids. This work demonstrates that D-amino acid degradation occurs largely through the concerted action of D-amino acid dehydrogenase, encoded by the dadA gene, and **D-serine dehydratase**, encoded by the dsdA gene. Deletion mutants of E. coli which lack these activities were constructed and compared against wild type strains in D-amino acid degradation. An E. coli dadA mutant reduced the degradation of D-methionine by one third, D-phenylalanine by two-thirds, and D-2-amino-butyric acid nearly completely. Even though the dadA mutant had no effect on D-serine degradation, a dadA dsdA double mutant of E. coli additionally reduced degradation of D-serine, as well as D-phenylalanine, almost entirely. These strains are appropriate hosts for whole cell biosynthesis of D-amino acids using general approaches such as the **hydantoinase** system.

```
=> d ibib abs l4 2-5
```

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1101249 CAPLUS
DOCUMENT NUMBER: 142:260023
TITLE: D-amino acid tolerant hosts for D-**hydantoinase** whole cell biocatalysts
AUTHOR(S): Turner, Robert J.; Aikens, John; Royer, Sylvain; DeFilippi, Louis; Yap, Abigail; Holzle, Denise; Somers, Neil; Fotheringham, Ian G.
CORPORATE SOURCE: DeCODE Genetics, Woodridge, IL, 60517, USA
SOURCE: Engineering in Life Sciences (2004), 4(6), 517-520
CODEN: ELSNAE; ISSN: 1618-0240
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Whole cell biocatalysts which enable the concerted use of D-**hydantoinase**, D-carbamoylase, and racemase enzymes are valuable for the production of D-amino acids. However, Escherichia coli host strains used for this purpose efficiently degrade D-amino acids. This work demonstrates that D-amino acid degradation occurs largely through the concerted action of D-amino acid dehydrogenase, encoded by the dadA gene, and **D-serine dehydratase**, encoded by the dsdA gene. Deletion mutants of E. coli which lack these activities were constructed and compared against wild type strains in D-amino acid degradation An E. coli dadA mutant reduced the degradation of D-methionine by one third, D-phenylalanine by two-thirds, and D-2-aminobutyric acid nearly completely. Even though the dadA mutant had no effect on D-serine degradation, a dadA double mutant of E. coli addnl. reduced degradation of D-serine, as well as D-phenylalanine, almost entirely. These strains are appropriate hosts for whole cell biosynthesis of D-amino acids using general approaches such as the **hydantoinase** system.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:389629 CAPLUS
DOCUMENT NUMBER: 140:405577
TITLE: D-amino acid production by genetically engineered Escherichia coli
INVENTOR(S): May, Oliver; Buchholz, Stefan; Schwarm, Michael; Drauz, Karlheinz; Turner, Robert J.; Fotheringham, Ian
PATENT ASSIGNEE(S): Degussa A.-G., Germany
SOURCE: Ger. Offen., 17 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10251184	A1	20040513	DE 2002-10251184	20021104
CA 2511751	AA	20040521	CA 2003-2511751	20031015
WO 2004042047	A1	20040521	WO 2003-EP11432	20031015

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1558727 A1 20050803 EP 2003-775186 20031015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRIORITY APPLN. INFO.: DE 2002-10251184 A 20021104
WO 2003-EP11432 W 20031015

AB A recombinant escherichia coli strain and a process is provided for the biosynthesis of D-amino acids. In particular, an E. coli strain is provided which has been transformed with the genes hyuC and hyuD which encode D-carbamoylase and D-**hydantoinase** resp. Addnl. in the same strain either one or both of the genes dadA and dsdA which encode D-amino oxidase and D-serine hydratase, were inactivated by site-directed mutagenesis. Selected mutants can produce D-methionine, D-phenylalanine, D-α-aminobutyric acid and D-serine.

L4 ANSWER 4 OF 5 LIFESCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 2005:43170 LIFESCI
TITLE: D-Amino Acid Tolerant Hosts for D-**Hydantoinase** Whole Cell Biocatalysts
AUTHOR: Turner, R.J.; Aikens, J.; Royer, S.; DeFilippi, L.; Yap, A.; Holzle, D.; Somers, N.; Fotheringham, I.G.
CORPORATE SOURCE: deCODE Genetics, 2501 Davey Road, Woodridge IL 60517, USA; E-mail: embra1@mac.com
SOURCE: Engineering in Life Sciences [Eng. Life Sci.], (20040000) vol. 4, no. 6, pp. 517-520.
ISSN: 1618-0240.
DOCUMENT TYPE: Journal
FILE SEGMENT: W2
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Whole cell biocatalysts which enable the concerted use of D-**hydantoinase**, D- carbamoylase, and racemase enzymes are valuable for the production of D-amino acids. However, Escherichia coli host strains used for this purpose efficiently degrade D-amino acids. This work demonstrates that D-amino acid degradation occurs largely through the concerted action of D-amino acid dehydrogenase, encoded by the dadA gene, and **D-serine dehydratase**, encoded by the dsdA gene. Deletion mutants of E. coli which lack these activities were constructed and compared against wild type strains in D-amino acid degradation. An E. coli dadA mutant reduced the degradation of D-methionine by one third, D-phenylalanine by two-thirds, and D-2-aminobutyric acid nearly completely. Even though the dadA mutant had no effect on D-serine degradation, a dadA dsdA double mutant of E. coli additionally reduced degradation of D-serine, as well as D-phenylalanine, almost entirely. These strains are appropriate hosts for whole cell biosynthesis of D-amino acids using general approaches such as the **hydantoinase** system.

L4 ANSWER 5 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005006929 EMBASE
TITLE: D-amino acid tolerant hosts for D-**hydantoinase** whole cell biocatalysts.
AUTHOR: Turner R.J.; Aikens J.; Royer S.; DeFilippi L.; Yap A.; Holzle D.; Somers N.; Fotheringham I.G.
CORPORATE SOURCE: I.G. Fotheringham, deCODE Genetics, 2501 Davey Road, Woodridge, IL 60517, United States. embra1@mac.com
SOURCE: Engineering in Life Sciences, (2004) Vol. 4, No. 6, pp. 517-520. .
Refs: 10
ISSN: 1618-0240 CODEN: ELSNAE
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050113
Last Updated on STN: 20050113

AB Whole cell biocatalysts which enable the concerted use of D-**hydantoinase**, D-carbamoylase, and racemase enzymes are valuable for the production of D-amino acids. However, Escherichia coli host strains used for this purpose efficiently degrade D-amino acids. This work demonstrates that D-amino acid degradation occurs largely through the concerted action of D-amino acid dehydrogenase, encoded by the dadA gene, and **D-serine dehydratase**, encoded by the dsdA gene. Deletion mutants of E. coli which lack these activities were constructed and compared against wild type strains in D-amino acid degradation. An E. coli dadA mutant reduced the degradation of D-methionine by one third, D-phenylalanine by two-thirds, and D-2-amino-butyric acid nearly completely. Even though the dadA mutant had no effect on D-serine degradation, a dadA dsdA double mutant of E. coli additionally reduced degradation of D-serine, as well as D-phenylalanine, almost entirely. These strains are appropriate hosts for whole cell biosynthesis of D-amino acids using general approaches such as the **hydantoinase** system. .COPYRGT. 2004 Wiley-VCH Verlag GmbH & Co. KGaA.

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NEWS 7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 11	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 12	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 13	JAN 30	Saved answer limit increased
NEWS 14	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA

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FULL ESTIMATED COST	0.21	0.21

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FILE 'AGRICOLA' ENTERED AT 14:21:54 ON 06 FEB 2006

FILE 'JICST-EPLUS' ENTERED AT 14:21:54 ON 06 FEB 2006
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FILE 'EMBASE' ENTERED AT 14:21:54 ON 06 FEB 2006
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=> s hydantoin? and N-carbamoylamino (w) acid?
L1 38 HYDANTOIN? AND N-CARBAMOYLAMINO (W) ACID?

=> s hydantoin?
L2 20424 HYDANTOIN?

=> s N-carbamoylamino (w) acid?
L3 79 N-CARBAMOYLAMINO (W) ACID?

=> s d-amino (w) acid (w) oxidase and mutated
L4 52 D-AMINO (W) ACID (W) OXIDASE AND MUTATED

=> s l2 and l4
L5 0 L2 AND L4

=> s l4 and l3
L6 0 L4 AND L3

=> s d-amino (w) acid (w) oxidase
L7 6125 D-AMINO (W) ACID (W) OXIDASE

=> s l2 and l7
L8 25 L2 AND L7

=> s l7 and l3
L9 0 L7 AND L3

=> s N-carbamoyl-d-amino (w) acid?
L10 131 N-CARBAMOYL-D-AMINO (W) ACID?

=> s l7 and l10
L11 1 L7 AND L10

=> d ibib abs l11

L11 ANSWER 1 OF 1 MEDLINE on STN
ACCESSION NUMBER: 2002053339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11778878

TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in hydantoin degradation.
AUTHOR: Hils M; Munch P; Altenbuchner J; Syldatk C; Mattes R
CORPORATE SOURCE: Institute of Industrial Genetics, University of Stuttgart, Germany.
SOURCE: Applied microbiology and biotechnology, (2001 Dec) 57 (5-6) 680-8.
Journal code: 8406612. ISSN: 0175-7598.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF335479
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020717
Entered Medline: 20020716

AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-hydantoinase, D-carbamoylase and putative hydantoin racemase, D-**amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the hydantoin utilization genes showed similarities to genes involved in transposition. Expression of the D-hydantoinase and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased hydantoinase and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low hydantoinase activity remaining after inactivation of the D-hydantoinase gene indicated the presence of a second hydantoinase-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned hydantoin utilization genes were found to be localized on the 190 kb plasmid.

=> d ibib l8 1-25

L8 ANSWER 1 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2003345484 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12876794
TITLE: Microbial/enzymatic synthesis of chiral drug intermediates.
AUTHOR: Patel R N
CORPORATE SOURCE: Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, New Jersey 08903, USA.
SOURCE: Advances in applied microbiology, (2000) 47 33-78. Ref: 107
Journal code: 0370413. ISSN: 0065-2164.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030725
Last Updated on STN: 20030822
Entered Medline: 20030821

L8 ANSWER 2 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2002053339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11778878
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation.
AUTHOR: Hils M; Munch P; Altenbuchner J; Syldatk C; Mattes R

CORPORATE SOURCE: Institute of Industrial Genetics, University of Stuttgart, Germany.
SOURCE: Applied microbiology and biotechnology, (2001 Dec) 57 (5-6) 680-8.
Journal code: 8406612. ISSN: 0175-7598.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF335479
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020717
Entered Medline: 20020716

L8 ANSWER 3 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2001396162 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11337276
TITLE: Enzymatic synthesis of chiral intermediates for Omapatrilat, an antihypertensive drug.
AUTHOR: Patel R N
CORPORATE SOURCE: Enzyme Technology, Process Research & Development, Bristol-Myers Squibb Pharmaceutical Research Institute, One Squibb Drive, P.O. Box 191, New Brunswick, NJ 08903, USA.. patelr@bms.com
SOURCE: Biomolecular engineering, (2001 Jun) 17 (6) 167-82. Ref: 50
Journal code: 100928062. ISSN: 1389-0344.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20030313
Entered Medline: 20010712

L8 ANSWER 4 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2000044134 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10579533
TITLE: Enzymatic synthesis of L-6-hydroxynorleucine.
AUTHOR: Hanson R L; Schwinden M D; Banerjee A; Brzozowski D B; Chen B C; Patel B P; McNamee C G; Kodersha G A; Kronenthal D R; Patel R N; Szarka L J
CORPORATE SOURCE: Department of Microbial Technology, Bristol-Myers Squibb, New Brunswick, NJ 08903, USA.
SOURCE: Bioorganic & medicinal chemistry, (1999 Oct) 7 (10) 2247-52.
Journal code: 9413298. ISSN: 0968-0896.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991223

L8 ANSWER 5 OF 25 AGRICOLA Compiled and distributed by the National Agricultural Library of the Department of Agriculture of the United States of America. (2006) on STN

ACCESSION NUMBER: 2002:33817 AGRICOLA
DOCUMENT NUMBER: IND23268895
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation.
AUTHOR(S): Hils, M.; Munch, P.; Altenbuchner, J.; Syldatk, C.; Mattes, R.
AVAILABILITY: DNAL (QR1.E9)
SOURCE: Applied microbiology and biotechnology, Dec 2001. Vol. 57, No. 5/6. p. 680-688
Publisher: Berlin, Germany : Springer Verlag.
CODEN: AMBIDG; ISSN: 0175-7598
NOTE: Includes references
PUB. COUNTRY: Germany
DOCUMENT TYPE: Article
FILE SEGMENT: Non-U.S. Imprint other than FAO
LANGUAGE: English

L8 ANSWER 6 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:143603 BIOSIS
DOCUMENT NUMBER: PREV200200143603
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation.
AUTHOR(S): Hils, M.; Muench, P.; Altenbuchner, J. [Reprint author]; Syldatk, C.; Mattes, R.
CORPORATE SOURCE: Institute of Industrial Genetics, University of Stuttgart, Allmandring 31, 70569, Stuttgart, Germany
Josef.Altenbuchner@po.uni-Stuttgart.de
SOURCE: Applied Microbiology and Biotechnology, (December, 2001) Vol. 57, No. 5-6, pp. 680-688. print.
CODEN: AMBIDG. ISSN: 0175-7598.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L8 ANSWER 7 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:295796 BIOSIS
DOCUMENT NUMBER: PREV200100295796
TITLE: Enzymatic synthesis of chiral intermediates for Omapatrilat, an antihypertensive drug.
AUTHOR(S): Patel, Ramesh N. [Reprint author]
CORPORATE SOURCE: Enzyme Technology, Process Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, One Squibb Drive, New Brunswick, NJ, 08903, USA
patelr@bms.com
SOURCE: Biomolecular Engineering, (June, 2001) Vol. 17, No. 6, pp. 167-182. print.
ISSN: 1389-0344.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002

L8 ANSWER 8 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:57917 BIOSIS
DOCUMENT NUMBER: PREV200000057917
TITLE: Biocatalytic synthesis of chiral intermediates for antiviral and antihypertensive drugs.
AUTHOR(S): Patel, Ramesh N. [Reprint author]
CORPORATE SOURCE: Department of Enzyme Technology, Process Research, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, USA

SOURCE: Journal of the American Oil Chemists' Society, (Nov., 1999) Vol. 76, No. 11, pp. 1275-1281. print.
CODEN: JAOCA7. ISSN: 0003-021X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Feb 2000
Last Updated on STN: 3 Jan 2002

L8 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:389629 CAPLUS
DOCUMENT NUMBER: 140:405577
TITLE: D-amino acid production by genetically engineered Escherichia coli
INVENTOR(S): May, Oliver; Buchholz, Stefan; Schwarm, Michael; Drauz, Karlheinz; Turner, Robert J.; Fotheringham, Ian
PATENT ASSIGNEE(S): Degussa A.-G., Germany
SOURCE: Ger. Offen., 17 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10251184	A1	20040513	DE 2002-10251184	20021104
CA 2511751	AA	20040521	CA 2003-2511751	20031015
WO 2004042047	A1	20040521	WO 2003-EP11432	20031015
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1558727	A1	20050803	EP 2003-775186	20031015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: DE 2002-10251184 A 20021104
WO 2003-EP11432 W 20031015

L8 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:216 CAPLUS
DOCUMENT NUMBER: 136:364581
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation
AUTHOR(S): Hils, M.; Muench, P.; Altenbuchner, J.; Syldatk, C.; Mattes, R.
CORPORATE SOURCE: Institute of Industrial Genetics, University of Stuttgart, Stuttgart, 70569, Germany
SOURCE: Applied Microbiology and Biotechnology (2001), 57(5-6), 680-688
CODEN: AMBIDG; ISSN: 0175-7598
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:435820 CAPLUS
DOCUMENT NUMBER: 135:121212
TITLE: Enzymatic synthesis of chiral intermediates for Omapatrilat, an antihypertensive drug
AUTHOR(S): Patel, Ramesh N.
CORPORATE SOURCE: Enzyme Technology, Process Research & Development, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, 08903, USA
SOURCE: Biomolecular Engineering (2001), 17(6), 167-182
CODEN: BIENFV; ISSN: 1389-0344
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:749882 CAPLUS
DOCUMENT NUMBER: 132:151526
TITLE: Biocatalytic synthesis of chiral intermediates for antiviral and antihypertensive drugs
AUTHOR(S): Patel, Ramesh N.
CORPORATE SOURCE: Department of Enzyme Technology, Process Research, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, 08903, USA
SOURCE: Journal of the American Oil Chemists' Society (1999), 76(11), 1275-1281
CODEN: JAOCA7; ISSN: 0003-021X
PUBLISHER: AOCS Press
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:151526
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:651925 CAPLUS
DOCUMENT NUMBER: 132:63181
TITLE: Enzymatic synthesis of L-6-hydroxynorleucine
AUTHOR(S): Hanson, R. L.; Schwinden, M. D.; Banerjee, A.; Brzozowski, D. B.; Chen, B.-C.; Patel, B. P.; McNamee, C. G.; Kodersha, G. A.; Kronenthal, D. R.; Patel, R. N.; Szarka, L. J.
CORPORATE SOURCE: Department of Microbial Technology, Bristol-Myers Squibb, New Brunswick, NJ, USA
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(10), 2247-2252
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:63181
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:166877 CAPLUS
DOCUMENT NUMBER: 98:166877
TITLE: Production of 1-[11C]-L-leucine for tomographic measurement of local protein synthesis in man
AUTHOR(S): Barrio, J. R.; Phelps, M. E.; Keen, R. E.; MacDonald, N. S.
CORPORATE SOURCE: Sch. Med., UCLA, Los Angeles, CA, USA
SOURCE: Nucl. Med. Biol. Adv., Proc. World Congr., 3rd (1983),

Meeting Date 1982, Volume 2, 2135-7. Editor(s): Raynaud, Claude. Pergamon: Oxford, UK.
CODEN: 49KXAW
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1979:6301 CAPLUS
DOCUMENT NUMBER: 90:6301
TITLE: A general method for the preparation of the D- or L-stereoisomers of 5-substituted **hydantoins**
AUTHOR(S): Kern, Brian A.; Reitz, Richard H.
CORPORATE SOURCE: Toxicol. Res., Dow Chem. Co., Midland, MI, USA
SOURCE: Agricultural and Biological Chemistry (1978), 42(6), 1275-8
CODEN: ABCHA6; ISSN: 0002-1369
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:431993 CAPLUS
DOCUMENT NUMBER: 63:31993
ORIGINAL REFERENCE NO.: 63:5735h,5736a-d
TITLE: Isolation, characterization, and structural elucidation of new amino acids from bottromycin A
AUTHOR(S): Nakamura, Shoshiro; Chikaike, Takeo; Yonehara, Hiroshi; Umezawa, Hamao
CORPORATE SOURCE: Univ. Tokyo
SOURCE: Chemical & Pharmaceutical Bulletin (1965), 13(5), 599-602
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

L8 ANSWER 17 OF 25 LIFESCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 2002:34182 LIFESCI
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation
AUTHOR: Hils, M.; Muench, P.; Altenbuchner, J.; Syldatk, C.; Mattes, R.
CORPORATE SOURCE: Institute of Industrial Genetics, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany
SOURCE: Applied Microbiology and Biotechnology [Appl. Microbiol. Biotechnol.], (20011200) vol. 57, no. 5-6, pp. 680-688. ISSN: 0175-7598.
DOCUMENT TYPE: Journal
FILE SEGMENT: J; W2
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 18 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:34028263 BIOTECHNO
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation
AUTHOR: Hils M.; Munch P.; Altenbuchner J.; Syldatk C.; Mattes R.
CORPORATE SOURCE: J. Altenbuchner, Institute of Industrial Genetics, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany.
E-mail: Josef.Altenbuchner@po.uni-Stuttgart.de
SOURCE: Applied Microbiology and Biotechnology, (2001), 57/5-6 (680-688), 34 reference(s)
CODEN: AMBIDG ISSN: 0175-7598

DOCUMENT TYPE: Journal; Article
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 19 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32416454 BIOTECHNO
TITLE: Enzymatic synthesis of chiral intermediates for Omapatrilat, an antihypertensive drug
AUTHOR: Patel R.N.
CORPORATE SOURCE: R.N. Patel, Enzyme Technology, Bristol-Myers Squibb Pharmaceutical, Research Institute, One Squibb Drive, New Brunswick, NJ 08903, United States.
E-mail: patelr@bms.com
SOURCE: Biomolecular Engineering, (2001), 17/6 (167-182), 50 reference(s)
CODEN: BIENFV ISSN: 1389-0344
PUBLISHER ITEM IDENT.: S1389034401000685
DOCUMENT TYPE: Journal; General Review
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 20 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2000:30801898 BIOTECHNO
TITLE: Microbial/enzymatic synthesis of chiral drug intermediates
AUTHOR: Patel R.N.
CORPORATE SOURCE: R.N. Patel, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, NJ 08903, United States.
SOURCE: Advances in Applied Microbiology, (2000), 47/- (33-78), 107 reference(s)
CODEN: ADAMAP ISSN: 0065-2164
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 21 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29486587 BIOTECHNO
TITLE: Enzymatic synthesis of L-6-hydroxynorleucine
AUTHOR: Hanson R.L.; Schwinden M.D.; Banerjee A.; Brzozowski D.B.; Chen B.-C.; Patel B.P.; McNamee C.G.; Kodersha G.A.; Kronenthal D.R.; Patel R.N.; Szarka L.J.
CORPORATE SOURCE: R.L. Hanson, Department of Microbial Technology, Bristol-Myers Squibb, One Squibb Drive, New Brunswick, NJ 08903, United States.
SOURCE: Bioorganic and Medicinal Chemistry, (1999), 7/10 (2247-2252), 19 reference(s)
CODEN: BMECEP ISSN: 0968-0896
PUBLISHER ITEM IDENT.: S0968089699001583
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 22 OF 25 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002012040 EMBASE
TITLE: Cloning and characterization of genes from Agrobacterium sp. IP I-671 involved in **hydantoin** degradation.
AUTHOR: Hils M.; Munch P.; Altenbuchner J.; Syldatk C.; Mattes R.
CORPORATE SOURCE: J. Altenbuchner, Institute of Industrial Genetics,

University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany. Josef.Altenbuchner@po.uni-Stuttgart.de
SOURCE: Applied Microbiology and Biotechnology, (2001) Vol. 57, No. 5-6, pp. 680-688. .
Refs: 34
ISSN: 0175-7598 CODEN: AMBIDG
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020117
Last Updated on STN: 20020117

L8 ANSWER 23 OF 25 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001168843 EMBASE
TITLE: Enzymatic synthesis of chiral intermediates for Omapatrilat, an antihypertensive drug.
AUTHOR: Patel R.N.
CORPORATE SOURCE: R.N. Patel, Enzyme Technology, Bristol-Myers Squibb Pharmaceutical, Research Institute, One Squibb Drive, New Brunswick, NJ 08903, United States. patelr@bms.com
SOURCE: Biomolecular Engineering, (2001) Vol. 17, No. 6, pp. 167-182. .
Refs: 50
ISSN: 1389-0344 CODEN: BIENFV
PUBLISHER IDENT.: S 1389-0344(01)00068-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010523
Last Updated on STN: 20010523

L8 ANSWER 24 OF 25 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2000381118 EMBASE
TITLE: Microbial/enzymatic synthesis of chiral drug intermediates.
AUTHOR: Patel R.N.
CORPORATE SOURCE: R.N. Patel, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, NJ 08903, United States
SOURCE: Advances in Applied Microbiology, (2000) Vol. 47, pp. 33-78. .
Refs: 107
ISSN: 0065-2164 CODEN: ADAMAP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20001116
Last Updated on STN: 20001116

L8 ANSWER 25 OF 25 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999361575 EMBASE
TITLE: Enzymatic synthesis of L-6-hydroxynorleucine.
AUTHOR: Hanson R.L.; Schwinden M.D.; Banerjee A.; Brzozowski D.B.; Chen B.-C.; Patel B.P.; McNamee C.G.; Kodersha G.A.; Kronenthal D.R.; Patel R.N.; Szarka L.J.

CORPORATE SOURCE: R.L. Hanson, Department of Microbial Technology, Bristol-Myers Squibb, One Squibb Drive, New Brunswick, NJ 08903, United States
SOURCE: Bioorganic and Medicinal Chemistry, (1999) Vol. 7, No. 10, pp. 2247-2252. .
Refs: 19
ISSN: 0968-0896 CODEN: BMECEP
PUBLISHER IDENT.: S 0968-0896(99)00158-3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19991104
Last Updated on STN: 19991104

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FULL ESTIMATED COST	96.71	96.92

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Feb 3, 2006 (20060203/UP).

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YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, AGRICOLA, BIOSIS, CAPLUS, LIFESCI, BIOTECHNO, EMBASE' - CONTINUE? (Y)/N:y

L8 ANSWER 1 OF 25 MEDLINE on STN

AB Biocatalytic processes were used to prepare chiral intermediates for pharmaceuticals. These include the following processes. Enzymatic synthesis of [4S-(4a,7a,10ab)]1-octahydro-5-oxo-4-[[(phenylmethoxy) carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid methyl ester (BMS-199541-01), a key chiral intermediate for synthesis of a new vasopeptidase inhibitor. Enzymatic oxidation of the epsilon-amino group of lysine in dipeptide dimer N2-[N[[(phenylmethoxy)carbonyl] L-homocysteinyl] L-lysine)1,1-disulfide (BMS-201391-01) to produce BMS-199541-01 using a novel L-lysine epsilon-aminotransferase from S. paucimobilis SC16113 was demonstrated. This enzyme was overexpressed in E. coli, and a process was developed using recombinant enzyme. The aminotransferase reaction required alpha-ketoglutarate as the amine acceptor. Glutamate formed during this reaction was recycled back to alpha-ketoglutarate by glutamate oxidase from S. noursei SC6007. Synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 5 to L-6-hydroxy norleucine 4 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of ketoacid 5, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine (readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin**, 6) with **D-amino acid oxidase** from porcine kidney or T. variabilis followed by reductive amination to convert the mixture to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess. Enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 7), one of three building blocks used for synthesis of a vasopeptidase inhibitor, was demonstrated using

phenylalanine dehydrogenase from T. intermedius. The reaction requires ammonia and NADH. NAD produced during the reaction was recycled to NADH by oxidation of formate to CO2 using formate dehydrogenase. Efficient synthesis of chiral intermediates required for total chemical synthesis of a beta 3 receptor agonist was demonstrated. These include: (a) microbial reduction of 4-benzyloxy-3-methanesulfonylamino-2'-bromoacetophenone 9 to corresponding (R)-alcohol 10 by S. paucimobilis SC16113, (b) enzymatic resolution of racemic alpha-methyl phenylalanine amide 11 and alpha-methyl-4-hydroxyphenylalanine amide 13 by amidase from M. neoaurum ATCC 25795 to prepare corresponding (S)-amino acids 12 and 14, and (c) asymmetric hydrolysis of methyl-(4-methoxyphenyl)-propanedioic acid ethyl diester 15 to corresponding (S)-monoester 16 by pig liver esterase. (S)[1-(acetoxyl)-4-(3-phenyl)butyl]phosphonic acid diethyl ester 21, a key chiral intermediate required for total chemical synthesis of BMS-188494 (an anticholesterol drug) was prepared by stereoselective acetylation of racemic [1-(hydroxy)-4-(3-phenyl)butyl]phosphonic acid diethyl ester 22 using G. candidum lipase. Lipase-catalyzed stereoselective acetylation of racemic 7-[N,N'-bis-(benzyloxy-carbonyl)N-(guanidinoheptanoyl)]-alpha-hydroxy-glycine 24 to corresponding S-(-)-acetate 25 was demonstrated. S-(-)-acetate 25 is a key intermediate for total chemical synthesis of (-)-15-deoxyspergualin 23, an immunosuppressive agent and antitumor antibiotic. Stereoselective microbial reduction of (1S)[3-chloro-2-oxo-1-(phenyl-methyl)propyl] carbamic acid, 1,1-dimethyl-ethyl ester 26 to corresponding chiral alcohol 27a (a key chiral intermediate for HIV protease inhibitors) was also demonstrated. Stereospecific enzymatic hydrolysis of racemic epoxide RS-1-[2',3'-dihydro benzo[b]furan-4'-yl]-1,2-oxirane 29 the corresponding R-diol 30 and unreacted chiral S-epoxide 28 was demonstrated using R. glutinis and A. niger. Dynamic resolution of racemic diol RS-1-[2',3'-dihydrobenzo[b]furan-4'-yl]-ethane-1,2-diol 32 to corresponding S-diol S-1-[2',3'-dihydrobenzo[b]furan-4'-yl]-ethane-1,2-diol 31 was demonstrated using C. boidinii and P. methanolica. Chiral (S)-epoxide 28 and (S)-diol 31 are key intermediates for a new prospective circadian modulator drug. Enzymatic resolution of racemic 2-pentanol and 2-heptanol by lipase B from Candida antarctica was demonstrated. S-(+)-2-pentanol is a key chiral intermediate required for synthesis of anti-Alzheimer's drugs.

L8 ANSWER 2 OF 25 MEDLINE on STN

AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-**hydantoinase**, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second **hydantoinase**-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

L8 ANSWER 3 OF 25 MEDLINE on STN

AB Biocatalytic processes were used to prepare chiral intermediates required for the synthesis of Omapatrilat 1 by three different routes. The synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 3 to L-6-hydroxynorleucine 2 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of

the ketoacid 3, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine [readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin** 4] with **D-amino acid oxidase** from porcine kidney or Trigonopsis variabilis followed by reductive amination to convert the mixture completely to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess (e.e.). The enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 5) was demonstrated using phenylalanine dehydrogenase (PDH) from T. intermedius. Phenylalanine dehydrogenase was cloned and overexpressed in Escherichia coli and Pichia pastoris. Using PDH from E. coli or P. pastoris, the enzymatic process was scale-up to prepare kg quantity of allysine ethylene acetal 5. The reaction yields of >94% and e.e. of >98% were obtained for allysine ethylene acetal 5. An enzymatic process was developed for the synthesis of [4S-(4a,7a,10ab)]1-octahydro-5-oxo-4 [[(phenylmethoxy)carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid [BMS-199541-01]. The enzymatic oxidation of the epsilon-amino group of lysine in the dipeptide dimer N(2)-[N[[(phenyl-methoxy)carbonyl] L-homocysteinyl] L-lysine)-1,1-disulphide [BMS-201391-01] to produce BMS-199541-01 using a novel L-lysine epsilon-aminotransferase (LAT) from Sphingomonas paucimobilis SC 16113 was demonstrated. This enzyme was overexpressed in E. coli and a process was developed using the recombinant enzyme.

L8 ANSWER 4 OF 25 MEDLINE on STN

AB L-6-Hydroxynorleucine, a key chiral intermediate used for synthesis of a vasopeptidase inhibitor, was prepared in 89% yield and > 99% optical purity by reductive amination of 2-keto-6-hydroxyhexanoic acid using glutamate dehydrogenase from beef liver. In an alternate process, racemic 6-hydroxynorleucine produced by hydrolysis of 5-(4-hydroxybutyl) **hydantoin** was treated with **D-amino acid oxidase** to prepare a mixture containing 2-keto-6-hydroxyhexanoic acid and L-6-hydroxynorleucine followed by the reductive amination procedure to convert the mixture entirely to L-6-hydroxynorleucine, with yields of 91 to 97% and optical purities of > 99%.

L8 ANSWER 5 OF 25 AGRICOLA Compiled and distributed by the National Agricultural Library of the Department of Agriculture of the United States of America. It contains copyrighted materials. All rights reserved. (2006) on STN

AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-**hydantoinase**, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second **hydantoinase**-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

L8 ANSWER 6 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-

hydantoinase, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second **hydantoinase**-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

L8 ANSWER 7 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AB Biocatalytic processes were used to prepare chiral intermediates required for the synthesis of Omapatrilat 1 by three different routes. The synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 3 to L-6-hydroxynorleucine 2 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of the ketoacid 3, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine (readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin** 4) with D-**amino acid oxidase** from porcine kidney or Trigonopsis variabilis followed by reductive amination to convert the mixture completely to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess (e.e.). The enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 5) was demonstrated using phenylalanine dehydrogenase (PDH) from T. intermedius. Phenylalanine dehydrogenase was cloned and overexpressed in Escherichia coli and Pichia pastoris. Using PDH from E. coli or P. pastoris, the enzymatic process was scale-up to prepare kg quantity of allysine ethylene acetal 5. The reaction yields of > 94% and e.e. of > 98% were obtained for allysine ethylene acetal 5. An enzymatic process was developed for the synthesis of (4S-(4a,7a,10ab))1-octahydro-5-oxo-4 (((phenylmethoxy)carbonyl)amino)-7H-pyrido-(2,1-b) (1,3)thiazepine-7-carboxylic acid (BMS-199541-01). The enzymatic oxidation of the epsilon-amino group of lysine in the dipeptide dimer N2-(N(((phenyl-methoxy)carbonyl) L-homocysteinyl) L-lysine)-1,1-disulphide (BMS-201391-01) to produce BMS-199541-01 using a novel L-lysine epsilon-aminotransferase (LAT) from Sphingomonas paucimobilis SC 16113 was demonstrated. This enzyme was overexpressed in E. coli and a process was developed using the recombinant enzyme.

L8 ANSWER 8 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AB The chiral intermediate (1S,2R) (3-chloro-2-hydroxy-1-(phenylmethyl)propyl) carbamic acid, 1,1-dimethylethyl ester 2a was prepared for the total synthesis of a human immunodeficiency virus protease inhibitor, BMS-186318. The stereoselective reduction of (1S) (3-chloro-2-oxo-1 (phenylmethyl)propyl) carbamic acid, 1,1-dimethylethyl ester 1 was carried out using microbial cultures, among which Streptomyces nodosus SC 13149 efficiently reduced 1 to 2a. A reaction yield of 80%, enantiomeric excess (e.e.) of 99.8%, and diastereomeric purity of 99% were obtained for chiral alcohol 2a. Chiral L-6-hydroxy norleucine 3, an intermediate in the synthesis of antihypertensive drug, was prepared by reductive amination of 2-keto-6-hydroxyhexanoic acid 4 using beef liver glutamate dehydrogenase. The cofactor NADH required for this reaction was regenerated using glucose dehydrogenase from Bacillus sp. A reaction yield of 80% and e.e. of 99.5% were obtained for L-6-hydroxynorleucine 3. To avoid the lengthy chemical synthesis of the ketoacid, a second route

was developed in which racemic 6-hydroxynorleucine (readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin** 5) was treated with **D-amino acid oxidase** from Trigonopsis variabilis to selectively convert the D-isomer of racemic 6-hydroxynorleucine to 2-keto-6-hydroxyhexanoic acid 4 and L-6-hydroxynorleucine 3. Subsequently, the 2-keto-6-hydroxyhexanoic acid 4 was converted to L-6-hydroxynorleucine by reductive amination using glutamate dehydrogenase. A reaction yield of 98% and an e.e. of 99.5% were obtained.

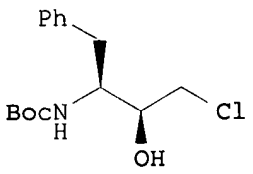
L8 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
AB A recombinant escherichia coli strain and a process is provided for the biosynthesis of D-amino acids. In particular, an E. coli strain is provided which has been transformed with the genes hyuC and hyuD which encode D-carbamoylase and D-**hydantoinase** resp. Addnl. in the same strain either one or both of the genes dadA and dsdA which encode D-amino oxidase and D-serine hydratase, were inactivated by site-directed mutagenesis. Selected mutants can produce D-methionine, D-phenylalanine, D-α-aminobutyric acid and D-serine.

L8 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-**hydantoinase**, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, resp., in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second **hydantoinase**-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

L8 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
AB A review with 50 refs. Biocatalytic processes were used to prepare chiral intermediates required for the synthesis of Omapatrilat 1 by three different routes. The synthesis and enzymic conversion of 2-keto-6-hydroxyhexanoic acid 3 to L-6-hydroxynorleucine 2 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of the ketoacid 3, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine [readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin** 4] with D-**amino acid oxidase** from porcine kidney or Trigonopsis variabilis followed by reductive amination to convert the mixture completely to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess (e.e.). The enzymic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allylsine ethylene acetal, 5) was demonstrated using phenylalanine dehydrogenase (PDH) from T. intermedius. Phenylalanine dehydrogenase was cloned and overexpressed in Escherichia coli and Pichia pastoris. Using PDH from E. coli or P. pastoris, the enzymic process was scale-up to prepare kg quantity of allylsine ethylene acetal 5. The reaction yields of > 94% and e.e. of > 98% were obtained for allylsine ethylene acetal 5. An enzymic process was developed for the synthesis of [4S-(4a, 7a, 10ab)]1-octahydro-5-oxo-4 [[(phenylmethoxy)carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid [BMS-199541-01]. The enzymic oxidation of the ε-amino group of lysine in the dipeptide dimer

N2-(N[[(phenyl-methoxy)carbonyl] L-homocysteinyl] L-lysine)-1,1-disulfide [BMS-201391-01] to produce BMS-199541-01 using a novel L-lysine ε-aminotransferase (LAT) from Sphingomonas paucimobilis SC 16113 was demonstrated. This enzyme was overexpressed in E. coli and a process was developed using the recombinant enzyme.

L8 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
GI



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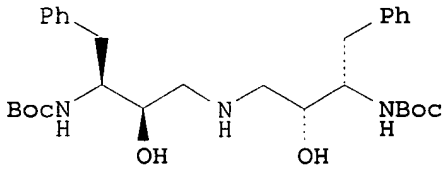

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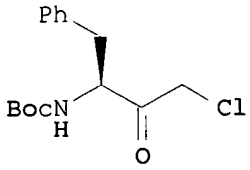

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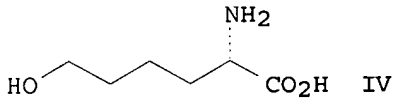

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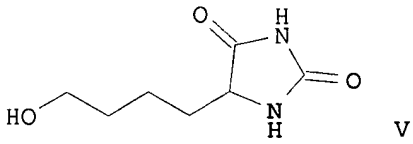


V

AB Nonracemic hydroxyphenylmethylpropyl carbamate I was prepared for the total synthesis of human immunodeficiency virus protease inhibitor II (BMS-186318). The stereoselective reduction of chloromethyl phenethyl ketone (1S)-III was carried out using microbial cultures, among which Streptomyces nodosus SC 13149 efficiently reduced III to I. A reaction yield of 80%, enantiomeric excess (e.e.) of 99.8%, and diastereomeric purity of 99% were obtained for chiral alc. I. Chiral L-6-hydroxy norleucine IV, an intermediate in the synthesis of an antihypertensive drug, was prepared by reductive amination of HO(CH2)4COCO2H using beef liver glutamate dehydrogenase. The cofactor NADH required for this reaction was regenerated using glucose dehydrogenase from Bacillus sp. A reaction yield of 80% and e.e. of 99.5% were obtained for IV. To avoid the lengthy chemical synthesis of the ketoacid, a second route was developed in which racemic IV [readily available from hydrolysis of **hydantoin** V] was treated with **D-amino acid oxidase** from Trigonopsis variabilis to selectively convert the D-isomer of IV to HO(CH2)4COCO2H and nonracemic IV. Subsequently, HO(CH2)4COCO2H was converted to L-6-hydroxynorleucine by reductive amination using glutamate dehydrogenase. A reaction yield of 98% and an e.e. of 99.5% were obtained.

L8 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
AB L-6-Hydroxynorleucine (I), a key chiral intermediate used for synthesis of a vasopeptidase inhibitor, was prepared in 89% yield and >99% optical purity by reductive amination of 2-keto-6-hydroxyhexanoic acid using glutamate dehydrogenase from beef liver. In an alternate process, racemic

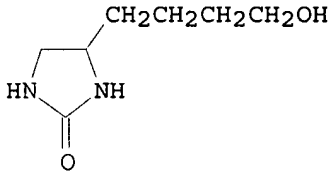
6-hydroxynorleucine produced by hydrolysis of 5-(4-hydroxybutyl) **hydantoin** was treated with **D-amino acid oxidase** to prepare a mixture containing 2-keto-6-hydroxyhexanoic acid and I, followed by the reductive amination procedure to convert the mixture entirely to I, with yields of 91-7% and optical purities of >99%.

L8 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

AB L-[1-11C]leucine was prepared by a modification of the Buecherer-Strecker reaction (Washburn, L.C., et al., 1979) for use in positron tomog. of brain protein synthesis in laboratory animals and man. The synthesis entails reacting H11CN with (NH4)2CO3 and isovaleraldehyde to form the alkyl **hydantoin**. This is hydrolyzed to form DL-[1-11C]leucine which reacted with an enzyme column containing **D-amino acid oxidase** and catalase. L-[1-11C]leucine is isolated by anion-exchange chromatog. and purified by membrane filtration.

L8 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

GI



I

AB Racemic (hydroxybutyl)**hydantoin** (DL-I) was hydrolyzed in aqueous Ba(OH)2 at 121° in an autoclave to give DL-HO(CH2)4CH(NH2)CO2H, which was digested with **D-amino acid oxidase** to give a mixture of L-HO(CH2)4CH(NH2)CO2H (II) and HO(CH2)4COCO2H. This mixture was separated by ion-exchange chromatog. and the resulting enantiomeric pure II underwent cyclization with KCNO to give L-I.

L8 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

AB cf. CA 62, 15381g. Bottromycin A (1 g.) and 20 ml. Ac2O heated 3 hrs. at 100° and the solution concentrated to small volume and refrigerated overnight gave crystalline N-(N-acetyl-3-methyl-3-phenylalanyl)-3-(2-thiazolyl)-β-alanine Me ester; the filtrate was evaporated to dryness, the residue refluxed 24 hrs. with 40 ml. constant boiling HCl, the hydrolyzate evaporated in vacuo, the residue dissolved in H2O, the solution neutralized with Amberlite IR-4B (OH type) and evaporated, and the residue subjected to chromatography on cellulose powder with the upper phase of 100:12:100 BuOH-H2O-AcOH (6-ml. fractions were collected) gave separated amino acid fractions. Fractions 6 and 7 combined and evaporated in vacuo gave 19 mg. 3-methyl-3-phenyl-L-alanine (I), m. 186-8° (EtOH), identified by paper chromatography (PC) and by its N.M.R. spectrum, not decomposed by **D-amino acid oxidase**; the N-dithiocarbethoxy derivative of I showed a pos. Cotton effect in optical rotary dispersion (O.R.D.) in MeOH. Fractions 14-26 evaporated in vacuo, the residue dissolved in a small amount MeOH by warming, and the solution cooled, diluted with Me2CO, and refrigerated gave 47 mg. new amino acid 2-amino-3,3-dimethylbutyric acid (II), sublimes at 210-18°, pKa 2.4 and 9.7, not decomposed by D-**amino acid oxidase**, its O.R.D. being of the L-amino acid type. Evaporation of fractions 28-34 gave 38 mg. L-valine, [α]20D 14° (c 1, H2O), [α]20D 32° (c 1, N HCl), identified by PC, ir spectrum, and [α]D. Fractions 35-42 evaporated, the impure residue dissolved in a small amount MeOH, and the solution filtered through C and diluted with Me2CO gave 18 mg. new amino acid cis-3-methyl-L-proline (III), needles, m. 218-22° (decomposition)

(shrinks at 190-200°); the filtrate concentrated in vacuo to small volume, diluted with Me2CO, and refrigerated overnight gave 27 mg. another crystalline form cis-III, prisms, m. 241-4° (decomposition), [α]18D -58° (c 1, H2O); both forms were shown to be identical by PC; the cis configuration of III followed from its N.M.R. spectrum, cis-III gave yellow ninhydrin and blue isatin reactions and showed a neg. reaction to **D-amino acid oxidase**; its N-dithiocarbethoxy derivative (IIIa) showed a pos. Cotton effect in O.R.D. Fractions 43-51 evaporated gave 12 mg. 3-(2-thiazolyl)-β-alanine (IV), m. 200-1° (MeOH), [α]18D 9° (c 1, H2O), identified by PC. Evaporation of fractions 98-120 gave glycine, identified by PC and its ir spectrum. To 12.9 mg. cis-III in 0.5 ml. H2O was added 0.2 ml. N NaOH and 0.007 ml. CS2, the mixture stirred magnetically 16 hrs. at room temperature in a stoppered flask, 0.009 ml. EtI added, the mixture stirred 8 hrs., extracted 3 times with 5 ml. Et2O, and acidified with dilute H2SO4, and the product isolated with Et2O to give 20 mg. IIIa. II was similarly converted into its N-dithiocarbethoxy derivative The ir spectra of I, II, both forms of cis-III, and IV and the N.M.R. spectra of II and cis-III were recorded.

L8 ANSWER 17 OF 25 LIFESCI COPYRIGHT 2006 CSA on STN

AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-**hydantoinase**, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second **hydantoinase**-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

L8 ANSWER 18 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN

AN 2001:34028263 BIOTECHNO

AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-**hydantoinase**, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second **hydantoinase**-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

L8 ANSWER 19 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN

AN 2001:32416454 BIOTECHNO
AB Biocatalytic processes were used to prepare chiral intermediates required for the synthesis of Omapatrilat 1 by three different routes. The synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 3 to L-6-hydroxynorleucine 2 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of the ketoacid 3, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine [readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin** 4] with **D-amino acid oxidase** from porcine kidney or Trigonopsis variabilis followed by reductive amination to convert the mixture completely to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess (e.e.). The enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 5) was demonstrated using phenylalanine dehydrogenase (PDH) from T. intermedius. Phenylalanine dehydrogenase was cloned and overexpressed in Escherichia coli and Pichia pastoris. Using PDH from E. coli or P. pastoris, the enzymatic process was scale-up to prepare kg quantity of allysine ethylene acetal 5. The reaction yields of >94% and e.e. of >98% were obtained for allysine ethylene acetal 5. An enzymatic process was developed for the synthesis of [4S-(4a,7a,10ab)]1-octahydro-5-oxo-4 [[(phenylmethoxy)carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid [BMS-199541-01]. The enzymatic oxidation of the ε-amino group of lysine in the dipeptide dimer N.sup.2-[N[[(phenyl-methoxy)carbonyl] L-homocysteinyl] L-lysine)-1,1-disulphide [BMS-201391-01] to produce BMS-199541-01 using a novel L-lysine ε-aminotransferase (LAT) from Sphingomonas paucimobilis SC 16113 was demonstrated. This enzyme was overexpressed in E. coli and a process was developed using the recombinant enzyme.

L8 ANSWER 20 OF 25 BIOTECHNO
AN 2000:30801898 BIOTECHNO
AB Biocatalytic processes were used to prepare chiral intermediates for pharmaceuticals. These include the following processes. Enzymatic synthesis of [4S-(4a,7a,10ab)]1-octahydro-5-oxo-4-[[(phenylmethoxy) carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid methyl ester (BMS-199541-01), a key chiral intermediate for synthesis of a new vasopeptidase inhibitor. Enzymatic oxidation of the ε-amino group of lysine in dipeptide dimer N.sup.2-[N[[(phenylmethoxy)carbonyl] L-homocysteinyl] L-lysine)1,1-disulfide (BMS-201391-01) to produce BMS-199541-01 using a novel L-lysine ε-aminotransferase from S. paucimobilis SC16113 was demonstrated. This enzyme was overexpressed in E. coli, and a process was developed using recombinant enzyme. The aminotransferase reaction required α-ketoglutarate as the amine acceptor. Glutamate formed during this reaction was recycled back to α-ketoglutarate by glutamate oxidase from S. noursei SC6007. Synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 5 to L-6-hydroxy norleucine 4 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of ketoacid 5, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine (readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin**, 6) with **D-amino acid oxidase** from porcine kidney or T. variabilis followed by reductive amination to convert the mixture to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess. Enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 7), one of three building blocks used for synthesis of a vasopeptidase inhibitor, was demonstrated using phenylalanine dehydrogenase from T. intermedius. The reaction requires ammonia and NADH. NAD produced during the reaction was recycled to NADH by oxidation of formate to CO.sub.2 using formate dehydrogenase. Efficient synthesis of chiral intermediates required for total chemical synthesis of a β3 receptor agonist was demonstrated. These include:

(a) microbial reduction of 4-benzyloxy-3-methanesulfonylamino-2'-bromo-acetophenone 9 to corresponding (R)-alcohol 10 by S. paucimobilis SC16113, (b) enzymatic resolution of racemic α-methyl phenylalanine amide 11 and α-methyl-4-hydroxyphenylalanine amide 13 by amidase from M. neoaurum ATCC 25795 to prepare corresponding (S)-amino acids 12 and 14, and (c) asymmetric hydrolysis of methyl-(4-methoxyphenyl)-propanedioic acid ethyl diester 15 to corresponding (S)-monoester 16 by pig liver esterase. (S)[1-(acetoxyl)-4-(3-phenyl)butyl]phosphonic acid diethyl ester 21, a key chiral intermediate required for total chemical synthesis of BMS-188494 (an anticholesterol drug) was prepared by stereoselective acetylation of racemic [1-(hydroxy)-4-(3-phenyl)butyl]phosphonic acid diethyl ester 22 using G. candidum lipase. Lipase-catalyzed stereoselective acetylation of racemic 7-[N,N'-bis-(benzyloxy-carbonyl)N-(guanidinoheptanoyl)]-α-hydroxy-glycine 24 to corresponding S-(-)-acetate 25 was demonstrated. S-(-)-acetate 25 is a key intermediate for total chemical synthesis of (-)-15-deoxyspergualin 23, an immunosuppressive agent and antitumor antibiotic. Stereoselective microbial reduction of (1S)[3-chloro-2-oxo-1-(phenyl-methyl)propyl] carbamic acid, 1,1-dimethyl-ethyl ester 26 to corresponding chiral alcohol 27a (a key chiral intermediate for HIV protease inhibitors) was also demonstrated. Stereospecific enzymatic hydrolysis of racemic epoxide RS-1-{2',3'-dihydro benzo[b]furan-4'-yl}-1,2-oxirane 29 the corresponding R-diol 30 and unreacted chiral S-epoxide 28 was demonstrated using R. glutinis and A. niger. Dynamic resolution of racemic diol RS-1-{2',3'-dihydrobenzo[b]furan-4'-yl}-ethane-1,2-diol 32 to corresponding S-diol S-1-{2',3'-dihydro-benzo[b]furan-4'-yl}-ethane-1,2-diol 31 was demonstrated using C. boidinii and P. methanolica. Chiral (S)-epoxide 28 and (S)-diol 31 are key intermediates for a new prospective circadian modulator drug. Enzymatic resolution of racemic 2-pentanol and 2-heptanol by lipase B from Candida antarctica was demonstrated. S-(+)-2-pentanol is a key chiral intermediate required for synthesis of anti-Alzheimer's drugs.

L8 ANSWER 21 OF 25 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 1999:29486587 BIOTECHNO
AB L-6-Hydroxynorleucine, a key chiral intermediate used for synthesis of a vasopeptidase inhibitor, was prepared in 89% yield and >99% optical purity by reductive amination of 2-keto-6-hydroxyhexanoic acid using glutamate dehydrogenase from beef liver. In an alternate process, racemic 6- hydroxynorleucine produced by hydrolysis of 5-(4-hydroxybutyl) **hydantoin** was treated with **D-amino acid oxidase** to prepare a mixture containing 2-keto-6-hydroxyhexanoic acid and L-6-hydroxynorleucine followed by the reductive amination procedure to convert the mixture entirely to L-6-hydroxynorleucine, with yields of 91 to 97% and optical purities of >99%.

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AB Cloning and sequencing of a 7.1 kb DNA fragment from Agrobacterium sp IP I-671 revealed seven open reading frames (ORFs) encoding D-**hydantoinase**, D-carbamoylase and putative **hydantoin** racemase, **D-amino acid oxidase** and NAD(P)H-flavin oxidoreductase. Two incomplete ORFs flanking the **hydantoin** utilization genes showed similarities to genes involved in transposition. Expression of the D-**hydantoinase** and D-carbamoylase gene in Escherichia coli gave mainly inactive protein concentrated in inclusion bodies, whereas homologous expression on an RSF1010 derivative increased **hydantoinase** and D-carbamoylase activity 2.5-fold and 10-fold, respectively, in this strain. Inactivation of the D-carbamoylase gene in Agrobacterium sp IP I-671 led to a complete loss of detectable carbamoylase activity whereas the low **hydantoinase** activity remaining after inactivation of the D-**hydantoinase** gene indicated the presence of a second

hydantoinase-encoding gene. Two plasmids of 80 kb and 190 kb in size were identified by pulsed-field gel electrophoresis and the cloned **hydantoin** utilization genes were found to be localized on the 190 kb plasmid.

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AB Biocatalytic processes were used to prepare chiral intermediates required for the synthesis of Omapatrilat 1 by three different routes. The synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 3 to L-6-hydroxynorleucine 2 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of the ketoacid 3, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine [readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin** 4] with D-**amino acid oxidase** from porcine kidney or Trigonopsis variabilis followed by reductive amination to convert the mixture completely to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess (e.e.). The enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 5) was demonstrated using phenylalanine dehydrogenase (PDH) from T. intermedius. Phenylalanine dehydrogenase was cloned and overexpressed in Escherichia coli and Pichia pastoris. Using PDH from E. coli or P. pastoris, the enzymatic process was scale-up to prepare kg quantity of allysine ethylene acetal 5. The reaction yields of >94% and e.e. of >98% were obtained for allysine ethylene acetal 5. An enzymatic process was developed for the synthesis of [4S-(4a,7a,10ab)]1-octahydro-5-oxo-4 [[(phenylmethoxy)carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid [BMS-199541-01]. The enzymatic oxidation of the ε-amino group of lysine in the dipeptide dimer N(2)-[N[[(phenyl-methoxy)carbonyl] L-homocysteinyl] L-lysine)-1,1-disulphide [BMS-201391-01] to produce BMS-199541-01 using a novel L-lysine ε-aminotransferase (LAT) from Sphingomonas paucimobilis SC 16113 was demonstrated. This enzyme was overexpressed in E. coli and a process was developed using the recombinant enzyme. Copyright .COPYRGT. 2001 Elsevier Science B.V.

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AB Biocatalytic processes were used to prepare chiral intermediates for pharmaceuticals. These include the following processes. Enzymatic synthesis of [4S-(4a,7a,10ab)]1-octahydro-5-oxo-4-[[(phenylmethoxy) carbonyl]amino]-7H-pyrido-[2,1-b] [1,3]thiazepine-7-carboxylic acid methyl ester (BMS-199541-01), a key chiral intermediate for synthesis of a new vasopeptidase inhibitor. Enzymatic oxidation of the ε-amino group of lysine in dipeptide dimer N2-[N[[(phenylmethoxy)carbonyl] L-homocysteinyl] L-lysine)1,1-disulfide (BMS-201391-01) to produce BMS-199541-01 using a novel L-lysine ε-aminotransferase from S. paucimobilis SC16113 was demonstrated. This enzyme was overexpressed in E. coli, and a process was developed using recombinant enzyme. The aminotransferase reaction required α-ketoglutarate as the amine acceptor. Glutamate formed during this reaction was recycled back to α-ketoglutarate by glutamate oxidase from S. noursei SC6007. Synthesis and enzymatic conversion of 2-keto-6-hydroxyhexanoic acid 5 to L-6-hydroxy norleucine 4 was demonstrated by reductive amination using beef liver glutamate dehydrogenase. To avoid the lengthy chemical synthesis of ketoacid 5, a second route was developed to prepare the ketoacid by treatment of racemic 6-hydroxy norleucine (readily available from hydrolysis of 5-(4-hydroxybutyl) **hydantoin**, 6) with **D-amino acid oxidase** from porcine kidney or T. variabilis followed by reductive amination to convert the mixture to L-6-hydroxynorleucine in 98% yield and 99% enantiomeric excess. Enzymatic synthesis of (S)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid (allysine ethylene acetal, 7), one of three building blocks used for

synthesis of a vasopeptidase inhibitor, was demonstrated using phenylalanine dehydrogenase from T. intermedius. The reaction requires ammonia and NADH. NAD produced during the reaction was recycled to NADH by oxidation of formate to CO2 using formate dehydrogenase. Efficient synthesis of chiral intermediates required for total chemical synthesis of a β3 receptor agonist was demonstrated. These include: (a) microbial reduction of 4-benzyloxy-3-methanesulfonylamino-2'-bromo-acetophenone 9 to corresponding (R)-alcohol 10 by S. paucimobilis SC16113, (b) enzymatic resolution of racemic α-methyl phenylalanine amide 11 and α-methyl-4-hydroxyphenylalanine amide 13 by amidase from M. neoaurum ATCC 25795 to prepare corresponding (S)-amino acids 12 and 14, and (c) asymmetric hydrolysis of methyl-(4-methoxyphenyl)-propanedioic acid ethyl diester 15 to corresponding (S)-monoester 16 by pig liver esterase. (S)[1-(acetoxyl)-4-(3-phenyl)butyl]phosphonic acid diethyl ester 21, a key chiral intermediate required for total chemical synthesis of BMS-188494 (an anticholesterol drug) was prepared by stereoselective acetylation of racemic [1-(hydroxy)-4-(3-phenyl)butyl]phosphonic acid diethyl ester 22 using G. candidum lipase. Lipase-catalyzed stereoselective acetylation of racemic 7-[N,N'-bis-(benzyloxy-carbonyl)N-(guanidinoheptanoyl)]-α-hydroxy-glycine 24 to corresponding S-(-)-acetate 25 was demonstrated. S-(-)-acetate 25 is a key intermediate for total chemical synthesis of (-)-15-deoxyspergualin 23, an immunosuppressive agent and antitumor antibiotic. Stereoselective microbial reduction of (1S)[3-chloro-2-oxo-1-(phenyl-methyl)propyl] carbamic acid, 1,1-dimethyl-ethyl ester 26 to corresponding chiral alcohol 27a (a key chiral intermediate for HIV protease inhibitors) was also demonstrated. Stereospecific enzymatic hydrolysis of racemic epoxide RS-1-{2',3'-dihydro benzo[b]furan-4'-yl}-1,2-oxirane 29 the corresponding R-diol 30 and unreacted chiral S-epoxide 28 was demonstrated using R. glutinis and A. niger. Dynamic resolution of racemic diol RS-1-{2',3'-dihydrobenzo[b]furan-4'-yl}-ethane-1,2-diol 32 to corresponding S-diol S-1-{2',3'-dihydro-benzo[b]furan-4'-yl}-ethane-1,2-diol 31 was demonstrated using C. boidinii and P. methanolica. Chiral (S)-epoxide 28 and (S)-diol 31 are key intermediates for a new prospective circadian modulator drug. Enzymatic resolution of racemic 2-pentanol and 2-heptanol by lipase B from Candida antarctica was demonstrated. S-(+)-2-pentanol is a key chiral intermediate required for synthesis of anti-Alzheimer's drugs.

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AB L-6-Hydroxynorleucine, a key chiral intermediate used for synthesis of a vasopeptidase inhibitor, was prepared in 89% yield and >99% optical purity by reductive amination of 2-keto-6-hydroxyhexanoic acid using glutamate dehydrogenase from beef liver. In an alternate process, racemic 6-hydroxynorleucine produced by hydrolysis of 5-(4-hydroxybutyl) **hydantoin** was treated with **D-amino acid oxidase** to prepare a mixture containing 2-keto-6-hydroxyhexanoic acid and L-6-hydroxynorleucine followed by the reductive amination procedure to convert the mixture entirely to L-6-hydroxynorleucine, with yields of 91 to 97% and optical purities of >99%.